REMARKS

Applicants again gratefully acknowledge withdrawal of the previous obviousness rejection under 35 U.S.C. 103(a) based on CA 2,474,902 ("Elbe et al") taken alone or in combination with JP 08/176112 ("Kanji et al") and the obviousness-type double patenting rejection based on copending application Serial No. 10/502,994.

Applicants have amended Claims 18-20 to limit the claimed subject matter to embodiments in which R^6 represents $-COR^7$ or $-CONR^8R^9$ and have accordingly canceled Claim 29. Because Applicants have previously discussed and recent Office Actions have addressed the subject matter of the amended claims, Applicants respectfully submit that the amendments do not impose any additional burden on examination. The arguments that follow below are intended to reiterate and elaborate upon Applicants' position, particularly with respect to the sufficiency of their experimental data.

Allowable Subject Matter

Applicants gratefully acknowledge the indication in the Final Office Action that Claims 26, 28, and 29 stand only objected to as being dependent upon a rejected base claim but would be allowable if rewritten in proper independent form. Applicants again note for the convenience of the Examiner that Claim 26 is directed to embodiments of Claim 18 in which R^6 represents $-COR^7$ in which R^7 is limited to 4-(difluoromethyl)-2-methyl-1,3-thiazol-2-yl; Claim 28 is directed to embodiments of Claim 18 in which R^6 represents -CHO; and Claim 29 is directed to embodiments of Claim 18 in which R^6 represents specific alkyl or substituted alkyl groups, cycloalkyl groups, or sulfanyl, sulfinyl, or sulfonyl groups but not carbonyl-containing groups within the meaning of $-COR^7$. Although allowable, Applicants have canceled subject matter that encompasses Claim 29. Applicants reserve the right to file one or more continuations directed to the canceled subject matter. Applicants maintain that all pending claims, including the base claim, are allowable as written and thus have not amended Claims 26 and 28 as kindly suggested by the Examiner.

Declarations under 37 C.F.R. 1.132

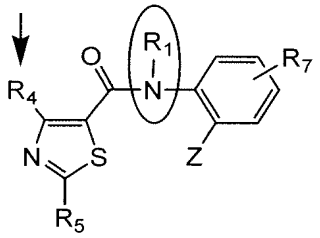
The Final Office Action at pages 3-4 appears to acknowledge the meaning of the two previously submitted Declarations under 37 C.F.R. 1.132 of Dr. Ulrike Wachendorff-Neumann (as discussed by Applicants in their previous Amendment dated March 9, 2009, at pages 9-10), in particular that Applicants' Example Set I of Dr. Wachendorff-Neumann's first Declaration shows a direct comparison between

their inventive compound of Example 9 and the compound of Example 4.32 of WO 02/059086 ("Walter et al") and that the remaining Example Sets of the first Declaration and Example Sets I and II of the second Declaration compare the inventive compounds of Applicants' Examples 9 and 6, respectively, with other known compounds. [Since the second Declaration relates only to alkyl-substituted compounds that are no longer part of Applicants' present claims, the following discussions will be limited to the first Declaration.] However, the Final Office Action continues to challenge the sufficiency of the test data. As will be discussed immediately below with respect to the obviousness rejection, Applicants maintain that their comparison experiments are appropriate.

Rejection under 35 U.S.C. 103

Claims 18-25, 27, and 29-33 stand rejected under 35 U.S.C. 103(a) as being unpatentable over WO 02/059086 ("Walter et al"), taken alone or in combination with JP 08/176112 ("Kanji et al"). Applicants again respectfully traverse.

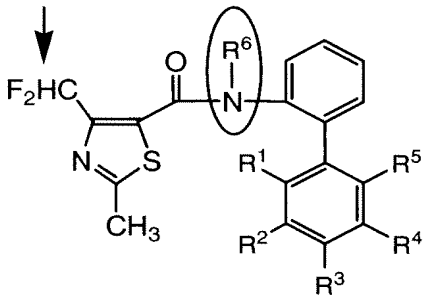
As fully discussed in Applicants' previous Amendments, **Walter et al** discloses certain microbicidal carboxamides, among the many types of which are compounds that can be represented by the formula



which is not shown as such in the reference but is based on the general disclosure of compounds in which A is a thiazole group (A3) and Q is a phenyl group (Q1). The definitions of groups R^5 and R^7, although relevant to the scope of the claims, are only peripheral to the central issue at hand and are not again described in detail. On the other hand, the meanings of the R_1 substituent on the bridging amide substituent (designated by an oval), the R_4 substituent on the thiazole ring (designated above by an arrow), and Z on the benzene ring are directly relevant and will again be discussed in detail. More specifically, group R^1 of the reference is either **(1)** one of three very specific unsaturated hydrocarbon groups having at least one carbon-carbon multiple bond, none of which is even remotely related to Applicants group R6, or **(2)** a carbonyl-containing group COR_3 in which R^3 is a narrowly defined set of

optionally substituted alkyl, alkoxy, alkylthio, alkenyloxy, or alkynyloxy groups. Group R_4 can be methyl, CF_3, CF_2H, CFH_2, Cl, or Br, with no statement of preference for any one such group. Finally, Z can be phenyl or halophenyl or various non-aromatic cyclic or acyclic groups. It may be noted, however, that the only thiazolecarboxamides specifically disclosed in Walter et al are those found in Table 4 (see pages 31-33), all of which have only CF_3 substituents, from which one might infer a preference for CF_3 substitution.

In contrast, Applicants' claimed thiazolylbiphenylamides of formula (I)



(I)

are characterized by a substituted bridging amide moiety (as shown by an oval) in which R^6 is limited to $-COR^7$ or $-CONR^8R^9$ groups and further characterized by a thiazole moiety in which the only halogenated alkyl substituent is CF_2H (as shown by an arrow). [Applicants note in particular their Claim 27, which is directed to compounds in which R^6 represents $-COR^7$ where R^7 in turn represents methyl, ethyl, cyclopropyl, or trifluoromethyl.] Applicants again submit that such compounds are patentably distinct from the carbonyl-containing compounds of Walter et al in which A is a thiazolyl group (A3), Q is a phenyl group (Q1), and the bridging amide group is substituted with COR_3 (shown above).

Applicants again submit that some of their claimed embodiments are indisputably patentably distinct from the compounds of Walter et al. ***First***, the Final Office Action at page 8 has again confirmed the allowability of claims that limit the carbonyl-containing substituents as specified in Claim 26 (in which R^6 represents $-COR^7$ to the extent that R^7 is limited to 4-(difluoromethyl)-2-methyl-1,3-thiazol-2-yl) and Claim 28 (in which R^6 represents formyl). ***Second***, Walter et al does not include amino groups within the definition of its R_3, which means that the reference also would not suggest compounds of Applicants' invention in which R^6 is $-CONR^8R^9$. Thus, the only remaining point of dispute relates to compounds the bridging amide nitrogen atom is substituted by a carbonyl group other than formyl. Even when

Walter et al discloses compounds in which R_3 is (halo)alkyl or (halo)alkoxy), Applicants submit that their claimed invention is patentable over Walter et al, even when combined with Kanji et al (as discussed below), when the overall teachings of the references are viewed in proper context.

Applicants again point out that it has well recognized that even structurally similar inventions can be patentably distinct under certain circumstances. E.g., *U.S. v. Adams*, 383 U.S. 39, 148 U.S.P.Q. 479 (1966). For example, a claimed invention is not rendered obvious merely because a reference discloses "compounds having a generic formula which would include [the claimed compounds] if proper selection from among the many possible variables were made as suitable for the claimed purpose." *Ex parte Strobel and Catino*, 160 U.S.P.Q. 352 (P.O. Bd. App. 1968); see also *In re Baird*, 29 U.S.P.Q.2d 1550, 1552 (Fed. Cir. 1994). This principle is particularly applicable where the properties exhibited by compounds in the relevant art are unpredictable and where, as here, comparative evidence supports a finding of non-obviousness. Applicants maintain that Walter et al does not describe the particular combination of structural features that characterize their claimed invention nor does the reference show even one example of an N-carbonyl-substituted compound in which A is a thiazole bearing a haloalkyl substituent R_4 other than CF_3. Only by picking and choosing from the host of possible groups disclosed in the reference could one in hindsight arrive at Applicants' specified combination of features. That is, to arrive at Applicants' claimed compounds, it would be necessary to **(A)** select only thiazoles (A3) from among the five heterocyclic structures of group A and *even then* only thiazoles in which substituent R_4 is CF_2H and **(B)** select only phenyl groups (Q1) from among the six ring structures of group Q and *even then* only phenyl groups in which substituent Z is phenyl or halophenyl and **(C)** select only COR_3 from among seven specific possibilities for group R_1 and *even then* only when R_3 represents only certain groups. Even if all of these variables can be found in Walter et al, the reference provides no indication that a selection of these specific features in combination would lead to enhanced efficacy. Applicants maintain that the failure of Walter et al to disclose compounds having the specific combination of structural and biological features that characterize their claimed invention is consistent with their invention being patentable.

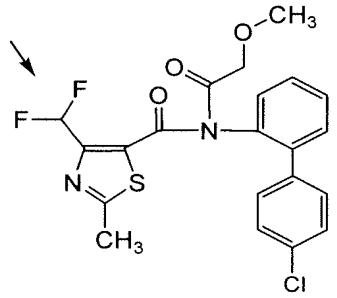
By way of further support for their position, Applicants again refer to the previously submitted first Declaration of 37 C.F.R. 1.132 of Dr. Ulrike Wachendorff-

Neumann, which provides comparison data that support the patentability of their claimed difluoromethyl-substituted thiazolylbiphenylamides over the compounds of the cited references. The Final Office Action, however, again challenges the sufficiency of the comparison data provided by Applicants. In response, Applicants again discuss the nature of their claimed compounds (with reference to specific structural formulas for clarity) and the test data supporting the patentability of their claimed compounds at issue.

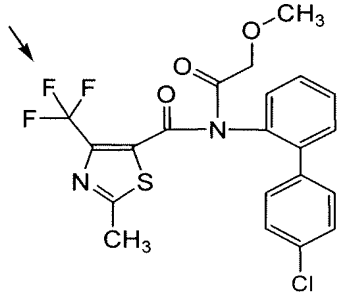
First, Applicants address the significance of difluoromethyl substitution on the thiazole moiety. The only thiazolecarboxamides specifically disclosed in Walter et al are those found in Table 4 (pages 31-33), all of which have only a CF_3 substituent on the thiazole ring. It is true that the reference in Tables 2, 7, and 9 discloses a few pyrazolecarboxamides having a CF_2H substituent on a pyrazole ring. However, the compounds in Tables 7 and 9 are not only not thiazoles, they are not even biphenyl compounds, both required features of Applicants' invention. Moreover, of the handful of pyrazoles shown in Table 2 as having CF_2H substituents on a pyrazole ring, only four – compounds 2.016, 2.017, 2.043, and 2.044 – are biphenyl compounds and of those, only two – compounds 2.043 and 2.044 – are biphenyl compounds having acyl substituents on the bridging amide group. Since no test results were provided for even one such difluoromethyl-substituted pyrazole compound, these compounds can hardly be considered to represent preferred embodiments or to suggest that CF_2H groups generally would be preferred substituents. Furthermore, since Walter et al provides no biological test data for any thiazole compound (i.e., where group A is thiazolyl group (A3)), Applicants maintain that those skilled in the art would not be led by the reference to expect thiazolyl compounds to be preferred (regardless of the nature of the R_4 group), much less that difluoromethyl-substituted thiazolylbiphenyl-amides such as claimed by Applicants would exhibit unexpectedly advantageous properties.

Applicants therefore maintain that the most reasonable comparison experiments would compare thiazolylbiphenylamides within the scope of their claimed invention with comparative thiazolecarboxamides falling within the scope of Walter et al. To this end, Applicants chose to show the significance of difluoromethyl substitution according to Example Set I of Dr. Wachendorff-Neumann's first Declaration. In particular, Example Set I provides a direct comparison between the

specifically disclosed inventive compound of Example 9 of Applicants' specification having the formula



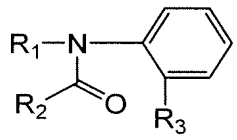
(see formula for Example 9 in Table 1 at pages 40-41 of the specification and Declarant's data shown in Example 2 of Table 1 of the Declaration) and the specifically disclosed comparison compound of Example 4.32 of Walter et al having the formula

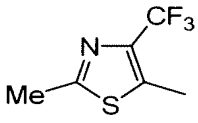


(see formula in Table 4 at page 33 of Walter et al and Declarant's data for this compound shown in Example 1 of Table 1 of the Declaration). The compounds are structurally identical except that Applicants' inventive compound has a difluoromethyl substituent on the thiazole moiety, whereas the comparison compound of Walter et al has a trifluoromethyl substituent on the thiazole moiety (shown by the arrows). Despite the ordinary expectation – based on the teachings of the reference – that the two substituents would be essentially interchangeable or even that CF_3 would be preferred (as discussed above), Applicants found that their inventive compound having a difluoromethyl substituent exhibited significantly enhanced biological activity compared to the corresponding compound of the reference having a trifluoromethyl substituent. Applicants submit that these results are directly relevant because they show an unexpected biological advantage associated with one of the required elements of their invention, that is, a CF_2H substituent on the thiazole moiety.

Second, Applicants address the significance of substituents on the bridging amide moiety. The Final Office Action at page 6 relies on Kanji et al, inter alia, as

teaching the interchangeability of the various substituents at the amide nitrogen atom of the disclosed thiazole-containing carboxamides. Even if this conclusion is taken as true for purposes of discussion, Applicants maintain that Kanji et al does not bridge the gap between Walter et al and their claimed invention. As has already been fully discussed in Applicants' previous Amendments, **Kanji et al** discloses carboxamides of the formula

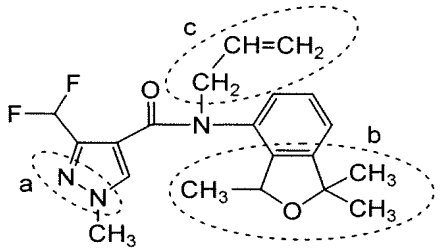


in which $\mathbf{R_1}$ can be any of a number of groups, including acyl groups of formulas -CO-R_4 (where R_4 can be alkyl, haloalkyl, or phenoxymethyl) or a second amide moiety -CO-NH-R_5 (where R_5 can be alkyl or phenyl), as well as certain ethers R_6 or alkyl groups R_7; $\mathbf{R_2}$ can be a variety of cyclic groups, including a specific trifluoromethyl-substituted thiazole moiety having the formula  ; and $\mathbf{R_3}$ can be any of a variety of cyclic or unsaturated groups, including phenyl. However, regardless of whether the reference teaches the interchangeability of amide substituents under some circumstances, Kanji et al does not even remotely suggest that the thiazole moiety can bear any haloalkyl substituent other than CF_3, which, as discussed above, Applicants have shown is associated with inferior properties relative to relevant compounds having the CHF_2 group that characterizes their claimed invention. In the absence of any suggestion of a difluoromethyl-substituted thiazolyl moiety, Kanji et al adds nothing that Walter et al does not already disclose that would lead those skilled in the art to their claimed invention.

Despite the demonstrated advantages associated with the combination of features that characterize Applicants' invention, the Final Office Action states that Applicants should have provided more data for more compounds. In particular, with reference to Applicants' Examples 1 and 8 (in which R^6 is acetyl) and Example 9 (in which R^6 is methoxyacetyl), the Final Office Action at pages 3-4 and again at page 5 suggests that Applicants should have augmented their arguments by comparing these inventive compounds to other compounds of Walter et al, with specific reference to Compounds 4.19, 4.20, 4.43, 4.44, and 7.03 of the reference. To aid in their discussion of these suggested comparisons, Applicants include in their

discussions below formulas for the compounds of Applicants' Examples 1, 8, and 9 and for the suggested Compounds 4.19, 4.20, 4.43, 4.44, and 7.03 of the reference, all of which are drawn with the same style and orientation (along with numbered arrows or ovals as explained below).

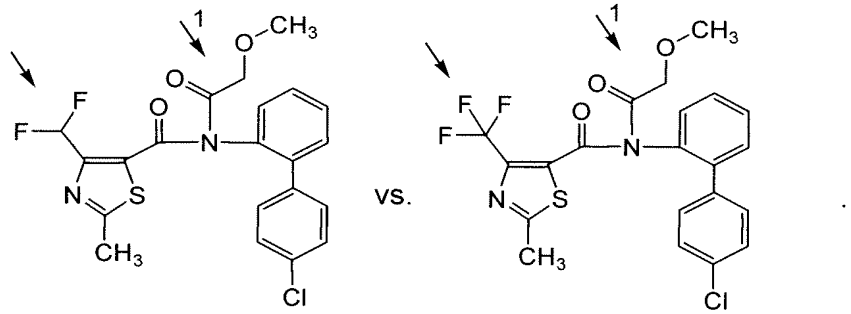
Applicants first again emphasize that Compound 7.03 of the reference, which has the following formula



Walter et al Cmpd. 7.03

is <u>not</u> a thiazolyl- <u>or</u> biphenyl-containing compound (see ovals a and b, respectively) <u>and</u> does not bear an acyl substituent on its bridging amide group (see oval c) and <u>thus has no possible relevance to the claims at issue</u>.

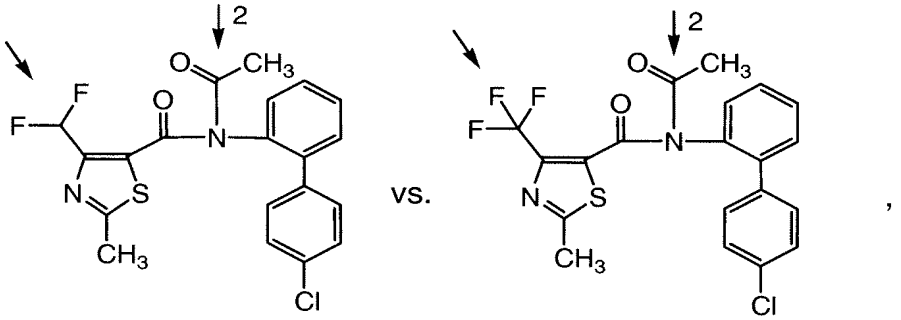
With respect to the other suggested comparison compounds, Applicants again note that the comparison experiments described in Dr. Wachendorff-Neumann's first Declaration were carried out using compounds having a <u>methoxyacetyl</u> amide substituent (shown by arrow 1), the only difference between the compounds being the respective difluoromethyl and trifluoromethyl substituents (shown by unnumbered arrows):



Inventive Ex. 9 vs. Walter et al Cmpd. 4.32

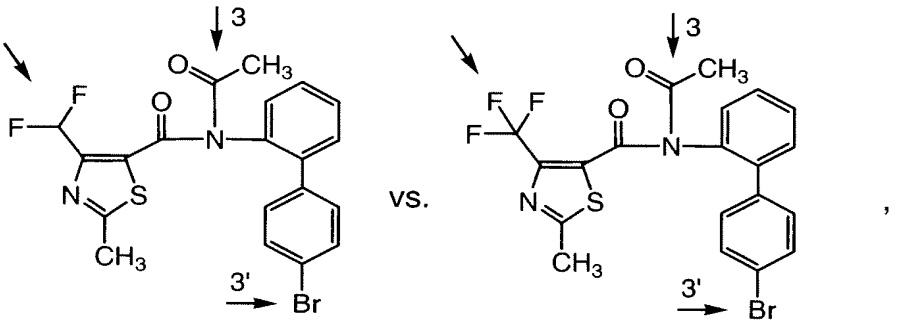
As discussed above, data obtained for these compounds clearly provide appropriate and supportive evidence of patentability.

Applicants assume that the suggested comparison experiment for the compound of their Example 8 would be carried out using the structurally similar Compound 4.19 of the reference



Inventive Ex. 8 Walter et al Cmpd. 4.19

where each compound has an acetyl amide substituent (shown by arrow 2), the only difference between the compounds being the respective difluoromethyl and trifluoromethyl substituents (again shown by unnumbered arrows), and further assume that the suggested comparison experiment for the compound of their Example 9 would be carried out using the structurally similar Compound 4.20 of the reference

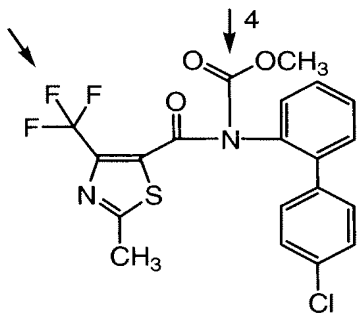


Inventive Ex. 1 Walter et al Cmpd. 4.20

where each compound again has an acetyl amide substituent (shown by arrow 3) but also have a bromine atom instead of a chlorine atom in the biphenyl moiety (shown by arrow 3'), the only difference between the compounds again being the respective difluoromethyl and trifluoromethyl substituents (again shown by unnumbered arrows). Applicants again point out that the purpose of their comparison experiments was to show the significance of the difluoromethyl substituent on the thiazole ring, not the effect of various amide substituents. Aside from the fact that the suggested comparisons presuppose that Applicants have access to the comparison compounds, Applicants fail to see how such additional comparisons would provide information that would be any more informative than the directly relevant comparison data already at hand. If one were to accept – as specifically suggested in the Final

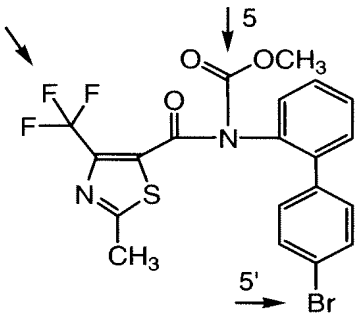
Office Action at pages 5-6 – that Kanji et al should be read as teaching the inter-changeability of the various acyl substituents at the amide nitrogen atom, then Applicants fail to see why they would need to carry out additional experiments using more than one acyl substituent on the bridging amide moiety.

Applicants are unsure what is to be gained by comparing any of their compounds of Examples 1, 8, or 9 with Compounds 4.43 and 4.44 of the reference.



Walter et al Cmpd. 4.43

or



Walter et al Cmpd. 4.44

where each compound has a methoxycarbonyl amide substituent (shown by arrows 4 and 5) and Compound 4.44 additionally has a bromine in the biphenyl moiety (shown by arrow 5'). If these compounds were to be compared with the compound of Applicants' Example 9 (in which the amide substituent is a methoxyacetyl group, not a methoxycarbonyl group), one would not be able to determine which of the variables – thiazole substituent? amide substituent? biphenyl substituent? all substituents? – would be responsible for any differences in test results. On the other hand, if these compounds were to be compared with the compounds of Applicants' Examples 8 and 1, respectively (where at least the halogen substituents on the biphenyl moieties would correspond), one would still not be able to determine which of the variables would be responsible for any differences in test results. Applicants therefore submit that any comparison of the compounds of their Examples 1, 8, or 9 with either of these compounds – which would be indirect at best – would not provide relevant information, much less information more informative than the direct comparison data already at hand. Furthermore, even if (as discussed above) one were to accept that Kanji et al can be read as teaching the interchangeability of the various acyl substituents at the amide nitrogen atom, Applicants again fail to see why additional experiments using yet another acyl substituent on the bridging amide moiety would be needed.

In sum, because the directly comparative experiments described in Dr. Wachendorff-Neumann's first Declaration show the significance of difluoromethyl substitution of the thiazole moiety, Applicants maintain that any other comparisons carried out using any other such compound of the reference, particularly with respect to substitution on the bridging amide, would be essentially merely duplicative and unnecessary.

Applicants therefore respectfully maintain that their invention is not rendered obvious by Walter et al, whether taken alone or in combination with Kanji et al.

In view of the preceding amendments and remarks, allowance of the claims is respectfully requested.

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